Central Sleep Apnea

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KEYWORDS

• Central sleep apnea • Mechanisms • Causes • Prevalence

Central apnea is caused by temporary failure in the pontomedullary pacemaker generating breathing rhythm. This results in the loss of ventilatory effort, and if it lasts 10 seconds or more it is defined as central apnea. During central apnea, there is no brainstem inspiratory neural output and the nerves innervating the inspiratory thoracic pump muscles are silent. Therefore, on the polysomnogram, central apnea is characterized by the absence of naso-oral airflow and thoracoabdominal excursions.

Central apnea as a polysomnographic finding could be either physiologic (normal) or have one of many pathologic causes (**Box 1**). The author and others have used a central apnea index (CAI) greater than or equal to 5 per hour of sleep as abnormal. However, the minimum number of events (apneas and hypopneas) required during sleep to represent a distinct disorder or syndrome (a condition associated with consequences; eg, insomnia, excessive daytime sleepiness, impaired quality of life, morbidity or mortality) is not known. The issue of a clinically significant threshold of central disordered breathing events is compounded by lack of inclusion of the number of hypopneas in the index (in contrast to the use of the obstructive apnea-hypopnea index [AHI], which is used to define the threshold), in part because of the difficulty in accurately distinguishing central hypopneas and obstructive hypopneas. In addition, the presence of central and obstructive apneas and hypopneas (mixed pattern of breathing) in the polysomnogram complicates accurate scoring. Examples of this mixed pattern of breathing include neuromuscular disorders, systolic heart failure, and opioid-associated sleep apnea. For these reasons, in patients with systolic heart failure, the author has used arbitrary polysomnographic criteria[1–3] to classify disordered breathing into either predominant central or obstructive sleep apnea. However, what the minimum central AHI should be to define the presence of a clinically significant sleep-related breathing disorder is not clear. In our studies of patients with heart failure, an AHI of 15 per hour or greater has been used arbitrarily, but this does not mean that it is the appropriate threshold. Further studies using outcomes are necessary to answer this question.

Box 1 shows the various physiologic and pathologic conditions associated with central sleep apnea.[4] The classification is in part based on the mechanisms and in part on the pathologic disorders associated with central sleep apnea. There is considerable overlap in disorders in which the pathologic process is diffuse, involving multiple sites. The mechanisms generating central sleep apnea are known in some but not all the disorders listed.

THE MECHANISMS OF GENESIS OF CENTRAL APNEA DURING SLEEP: THE APNEIC THRESHOLD AND DIMINISHED P_{CO_2} RESERVE

The mechanisms involved in the genesis of central apnea in sleep primarily relate to the removal of wakefulness drive to breathe and unmasking of a P_{CO_2}-sensitive apneic threshold,[5–8] a P_{CO_2} level below which rhythmical breathing ceases resulting in central apnea. Normally at onset sleep,

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Box 1
Central sleep apnea

I. Physiologic CSA

1. Sleep onset
2. Postarousal/postsigh
3. Phasic REM sleep

II. Hypopcapnic (nonhypercapnic) CSA[a]

1. Systolic heart failure
2. Idiopathic
3. Idiopathic pulmonary arterial hypertension
4. High altitude
5. Poststroke

III. Hypercapnic CSA[a]

1. Alveolar hypoventilation with normal pulmonary function
   a. Congenital central hypoventilation syndrome
   b. Primary chronic alveolar hypoventilation syndrome
2. Brainstem and spinal cord disorders encephalitis; tumors; infarcts; cervical cordotomy; anterior cervical spinal artery syndrome; neurodegenerative disorders; amyotrophic lateral sclerosis; multiple sclerosis; Chiari malformation
3. Muscular disorders; myotonic and Duchenne dystrophies; acid maltase deficiency; Guillain-Barré syndrome
4. Opioids

IV. CSA with endocrine disorders

1. Acromegaly
2. Hypothyrodism

V. CSA with OSA

1. A minor component of OSA
2. With CPAP therapy (complex sleep apnea)
3. Posttracheotomy

VI. CSA with upper airway disorders

Abbrevations: CPAP, continuous positive airway pressure; CSA, central sleep apnea; OSA, obstructive sleep apnea; REM, rapid eye movement.

[a] P_{CO_2}, however, may be normal at times.

Data from Javaheri S. Central sleep apnea. In: Lee-Chiong T, editor. Sleep medicine essentials. Hoboken (NJ): Wiley-Blackwell; 2009. p. 81–9.

ventilation decreases and P_{CO_2} increase by few a millimeters of mercury.

With removal of wakefulness drive to breathe, breathing during sleep is dominated by the metabolic control system, which is sensitive to small changes in P_{CO_2}. As long as the level of the prevailing P_{CO_2}, referred to as the eupneic P_{CO_2}, is more than the apneic P_{CO_2}, rhythmical breathing is maintained. However, if eupneic P_{CO_2} decreases below the apneic threshold P_{CO_2}, for example, after an arousal-related hyperventilation, breathing ceases. As a result of central apnea, P_{CO_2} increases and after it exceeds the apneic threshold P_{CO_2}, breathing resumes.

The difference between 2 P_{CO_2} set points, the eupneic P_{CO_2} minus the P_{CO_2} at the apneic threshold, referred to as the P_{CO_2} reserve, is a critical factor for development of central apnea. The less the P_{CO_2} reserve, the greater the likelihood of occurrence of central apnea. This is because small increases in ventilation could lower the eupneic P_{CO_2} to less than the apneic threshold. On the contrary, when apneic threshold P_{CO_2} is far away from the eucapnic P_{CO_2}, large ventilatory changes are necessary to lower the P_{CO_2} below the apneic threshold P_{CO_2} and therefore the likelihood of developing central apnea decreases.

CAUSES OF CENTRAL SLEEP APNEA

In this article, only selective causes of central sleep apnea are reviewed in detail (see **Box 1**). For other disorders, please see Ref.[4]

Physiologic Central Apnea

The conditions causing or associated with central sleep apnea in this category are considered normal sleep phenomena and, not surprisingly, the frequency of occurrence of such central apneas is normally minimal. Such central apneas are observed with onset of sleep, after an arousal or a sigh and occasionally during phasic rapid eye movement (REM) sleep.[9]

Eucapnic-hypocapnic (Nonhypercapnic) Central Sleep Apnea

These disorders are characterized by (1) an awake steady-state Pa_{CO_2} which is either within the low range of or less than the normal value (<36 mm Hg at sea level), and (2) increased ventilatory response to changes in P_{CO_2} and perhaps also to P_{O_2}.

During sleep, the prevailing P_{CO_2} may decrease to less than the apneic threshold (resulting in a central apnea), either because of inability to increase the P_{CO_2} or because the apneic threshold P_{CO_2} increases (eg, as a result of hypoxemia), or a combination of the 2. In addition, in these disorders (see **Box 1**), the hypercapnic ventilatory response is invariably increased above and below eupnoea. The increase in ventilatory response above eupnoea increases the likelihood of developing central apnea because any time an arousal

occurs, the immediate prearousal sleeping P_{CO_2} becomes hypercapnic for the aroused brain, and therefore, intense hyperventilation occurs that could drive the prevailing P_{CO_2} below the apneic threshold, causing a central apnea as sleep is resumed. Following central apnea, P_{CO_2} increases until an arousal recurs. In this way, the cycle of apnea-hyperpnea is perpetuated. The increase in CO_2 chemosensitivity below eupnoea is critical and has been best studied in systolic heart failure and during hypoxemia to explain the mechanism of high-altitude periodic breathing.

Systolic heart failure

Heart failure is a highly prevalent syndrome; it is estimated that about 5 to 6 million Americans, about 2% of the population, and 10% of those more than 65 years of age have heart failure. The approximate annual incidence is half a million.[10] Because heart failure is highly prevalent and central sleep apnea is common in the setting of the failing heart, heart failure is the most common cause of central sleep apnea in the general population (see later).

There is a distinct pattern of periodic breathing in systolic heart failure in that the breathing cycle has long crescendo decrescendo arms, as a result of a long arterial circulation time, a pathophysiologic feature of systolic heart failure. This pattern of periodic breathing is referred to as Hunter-Cheyne-Stokes breathing. John Hunter, a British surgeon, described it 37 years before John Cheyne's description.[11–14]

Prevalence of central apnea in systolic heart failure Studies[1–3,15–26] of patients with stable heart failure and left ventricular systolic dysfunction show that 40% to 80% have an AHI of 15 per hour or more. These indices include central and obstructive sleep apnea, events that commonly occur together during sleep in a patient with heart failure.

The largest and most systematic study[17] involved 100 ambulatory male patients with stable, treated heart failure. In this study, 114 consecutive eligible patients who were followed in a cardiology and a primary care clinic were asked to participate (88% recruitment) without regard to any symptom of sleep apnea. Using an AHI of 15 per hour or greater as the threshold, 49 patients (49% of all patients) had moderate to severe sleep apnea-hypopnea with an average index of 44 per hour. This index included central and obstructive events. In our studies about 10% of the patients were on β-blockers; however, the results of recent studies[23–26] that used an AHI of 15/h or more as the threshold are consistent with our report showing a high prevalence of sleep apnea, both central sleep apnea and obstructive sleep apnea despite use of β-blockers (up to 80% of the patients were on a β-blocker). Combining the results of these recent series[23–26] and our study[17] and using an AHI of 15/h of sleep as the threshold, there are 1250 consecutive patients with systolic heart failure, of which 52% have moderate to severe sleep apnea, 31% have central sleep apnea, and 21% have obstructive sleep apnea (**Fig 1**).

Mechanisms of central sleep apnea and periodic breathing in heart failure For simplicity, I make a distinction between mechanisms of central sleep apnea in heart failure (which have to do with increased CO_2 chemosensitivity below eupnoea, the P_{CO_2} reserve, and the lack of increase in P_{CO_2} with sleep onset) and the mechanisms mediating periodic breathing (which have to do with pathologic processes of heart failure).

Lack of increase in P_{CO_2} at sleep onset in systolic heart failure Normally, with onset of sleep, ventilation decreases and P_{CO_2} increases. This maintains the prevailing P_{CO_2} above the apneic threshold P_{CO_2}, and rhythmical breathing occurs. However, in some patients with heart failure, the prevailing awake P_{CO_2} does not increase at sleep onset.[27,28] This sets the stage for developing central apnea because of the proximity of the prevailing P_{CO_2} to the exposed apneic threshold.[8,27] The reason for the lack of increase in P_{CO_2} could be because of the lack of decrease in ventilation that normally occurs at sleep onset. Presumably, in patients with heart failure with severe left ventricular diastolic dysfunction (and stiff left ventricle which invariably accompanies systolic dysfunction), when in supine position venous return increases and pulmonary capillary pressure could increase. This results in a small increase in respiratory rate and ventilation, preventing the increase in P_{CO_2} normally observed.

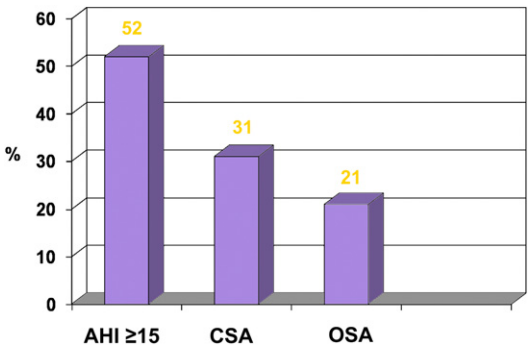

Fig. 1. Worldwide prevalence of sleep apnea in systolic heart failure(n = 1250 consecutive patients).

Increased CO_2 chemosensitivity below eupnea Several studies[29–31] have shown that patients with heart failure and low awake steady-state arterial P_{CO_2} have a high probability of developing central sleep apnea during sleep. It has been misinterpreted that it is this low awake P_{CO_2} that predisposes patients to central sleep apnea. In contrast, in the absence of an increase in CO_2 chemosensitivity below eupnoea, low awake P_{CO_2} per se should be protective in the sense that it decreases the likelihood of developing central apnea during sleep.

Why in the absence of increased CO_2 chemosensitivity below eupnoea, is low awake arterial P_{CO_2} per se protective? With nonhypoxic chemoreceptor stimulation such as metabolic acidosis or administration of almitrine (which stimulates carotid bodies), ventilation increases and P_{CO_2} decreases, without changing the chemosensitivity below eupnoea.[8] Under such conditions, the hyperbolic nature of the alveolar ventilation curve dictates a considerable increase in ventilation to decrease an already low P_{CO_2} below the apneic threshold P_{CO_2}. This is referred to as decreased plant gain (which is dictated by where Pa_{CO_2} resides on the alveolar ventilation equation curve) with an increase in $\triangle P_{CO_2}$ making development of central sleep apnea less probable.

In 1 study,[32] polysomnograms of 13 hypocapnic (Pa_{CO_2} <36 mm Hg, mean = 33 mm Hg) patients with heart failure, mean left ventricular ejection fraction of 23% were compared with those of 10 age-, gender-, and Pa_{CO_2}-matched hypocapnic (Pa_{CO_2} <36 mm Hg, mean = 32 mm Hg) patients with cirrhosis of the liver and normal ejection fraction (60%). In the former group, the mean apnea-hypopnea index was 28/h and central sleep apnea accounted for most of the breathing disorders; in the goup with cirrhosis, the mean AHI was 2/h and maximum CAI was 0.2/h. There were no significant differences in age, demographics, pulmonary function tests, Pa_{O_2}, Pa_{CO_2}, minute and alveolar ventilation, and ventilatory responses to CO_2 between the 2 groups. The authors concluded that in contrast to heart failure, presence of hypocapnia does not predict central apnea in cirrhosis. A similar conclusion regarding P_{CO_2} was reached in a study with acetazolamide. In a double-blind placebo-controlled crossover study[33] of 12 patients with heart failure, the CAI decreased significantly with acetazolamide (49 $\pm$ 28 vs 23 $\pm$ 21, mean $\pm$ standard deviation, P = .004). This despite the decrease in Pa_{CO_2}, from 38 to 34 mm Hg, P = .0003. These data along with findings in patients with cirrhosis emphasize that it is not the absolute value of the steady state that increases the likelihood of developing central apnea. Rather, it is the difference between the prevailing P_{CO_2} and the apneic threshold P_{CO_2} that is important.[8,27] As noted earlier, in the face of background increased stimulus to breathing, the difference between the prevailing P_{CO_2} minus apneic threshold P_{CO_2} widens.[8] This widening decreases the likelihood of developing central sleep apnea.

Then why in systolic heart failure is a low awake steady-state Pa_{CO_2} highly predictive for the development of central sleep apnea? In systolic heart failure, the low Pa_{CO_2} has to do with the severity of the ventricular diastolic dysfunction. Heart failure patients with hypocapnia have a more severe left ventricular diastolic dysfunction and a higher wedge pressure than patients with eucapnia patients.[19] Wedge pressure further increases in the supine position with the increase in venous return, stimulating J receptors. Consequently, such patients are not able to appropriately decrease their ventilation with sleep onset and their P_{CO_2} remains close to the apneic threshold.

Furthermore, via mechanisms yet to be discovered, pulmonary congestion increases the CO_2 chemosensitivity below eupnea and decreases the P_{CO_2} reserve increasing the likelihood of developing central sleep apnea.[34]

Although a low awake Pa_{CO_2} is highly predictive of central sleep apnea, it is not a prerequisite. Many patients with heart failure and central sleep apnea have normal awake Pa_{CO_2}.[15,35] What is important is the proximity of the apneic threshold to the Pa_{CO_2}.[8,27]

Another mechanism that increases the likelihood of developing central apnea during sleep and periodic breathing is enhanced ventilatory response to CO_2[36] which is discussed later.

Mechanisms of periodic breathing in systolic heart failure In systolic heart failure, central sleep apnea occurs in the background of periodic breathing characterized by long cresendo-decresendo ventilation arms, a reflection of prolonged circulation time. Increased arterial circulation time (which delays the transfer of information regarding changes in pulmonary capillary blood P_{O_2} and P_{CO_2} to the chemoreceptors), enhanced gain of the chemoreceptors (enhanced CO_2/O_2 chemosensitivity), and enhanced plant gain (a large change in Pa_{CO_2} for a small change in ventilation) collectively increase the likelihood of periodic breathing.[36–46]

In systolic heart failure, effective arterial circulation time is increased (as a result of pulmonary congestion, left atrial and ventricular enlargement, and diminished stroke volume); plant gain is also increased because of a low functional residual capacity (as a result of the presence of pleural

effusion, cardiomegaly, pulmonary congestion, or edema). In some patients hypercapnic ventilatory response is increased[36] and the chemoreceptors elicit a large ventilatory response whenever the partial pressure of carbon dioxide increases. The consequent intense hyperventilation, by driving the P_{CO_2} below the apneic threshold, results in central apnea. As a result of central apnea, P_{CO_2} increases and the cycles of hyperventilation and hypoventilation are maintained.

Because the aforementioned alterations are not sleep/wake specific, periodic breathing may occur during both states, although most frequently during sleep. During sleep, cardiac output decreases (further prolonging arterial circulation time), and functional residual capacity (supine position) and metabolic rate decrease enhancing the plant gain.

Treatment of central sleep apnea in heart failure is reviewed elsewhere[1–3,47–56] and is not discussed in this article.

Idiopathic central sleep apnea

This is a rare disorder[57,58] and a diagnosis of exclusion; other causes of central apnea noted in **Box 1**, including asymptomatic left ventricular dysfunction and multiple small infarcts that otherwise may be silent, should be excluded.

On the polysomnograph, idiopathic central sleep apnea is characterized by repetitive episodes of central apnea. However, the cycles of periodic breathing are shorter than those in systolic heart failure. Patients with idiopathic central sleep apnea are commonly older men, and may present with complaints of restless sleep, insomnia, and/or daytime symptoms such as sleepiness and fatigue related to insomnia, sleep fragmentation, and arousals.

Idiopathic central apnea in patients with idiopathic central apnea commonly have a low arterial P_{CO_2}, and increased hypercapnic ventilatory response[58,59] during wakefulness, which facilitates development of central apnea during sleep.

Although there are no randomized therapeutic trials, 2 nonrandomized open studies[59,60] have shown efficacy of acetazolamide in the treatment of idiopathic central sleep apnea. These results are consistent with the results of the double-blind placebo-controlled study on systolic heart failure showing the efficacy of acetazolamide in the treatment of central sleep apnea.[33]

Bilevel positive airway pressure devices are not recommended for treatment of central sleep apnea of any cause because by lowering the prevailing P_{CO_2} below the apneic threshold these devices could worsen central apnea.[61] New generation servo ventilators, however, should be effective.

Idiopathic pulmonary arterial hypertension

This disorder is characterized by pulmonary arterial hypertension with normal pulmonary capillary pressure. Genetic associations have been found.[62]

In the more advanced hemodynamic state of this disorder, there is severe pulmonary arterial hypertension, right ventricular failure, and diminished cardiac output. In 1 study[63] of 20 patients with idiopathic pulmonary artery hypertension (3 men and 17 women), 6 had moderately severe sleep apnea with an AHI of 37/h resulting in desaturation. The mean Pa_{CO_2} did not significantly differ between the 2 groups, but patients with periodic breathing had significantly more hemodynamic abnormalities than those without. Presumably, diminished stroke volume and increased arterial circulation time were the underlying mechanisms in mediating periodic breathing in this disorder.

In the study of Schultz and colleagues,[63] 3 out of the 3 men, but only 3 of 17 women had periodic breathing. This gender distribution is similar to that in systolic heart failure, and may have to do with gender differences in apneic threshold P_{CO_2}.[64,65]

For the treatment of central sleep apnea in idiopathic pulmonary arterial hypertension, the author recommends nocturnal supplemental nasal oxygen.[63] In 1 patient with idiopathic pulmonary hypertension, hypocapnia, and low cardiac output, central sleep apnea was eliminated after lung transplantation.[66] In another case report[67] use of bilevel positive airway pressure therapy was associated with death, although cause and effect cannot be proved, several possibilities including worsening of central sleep apnea and reduction in cardiac output with use of a bilevel device may be speculated. In general, the author does not recommend use of bilevel device to treat central sleep apnea.[68]

However, obstructive sleep apnea is a known cause of secondary pulmonary hypertension (for review see Ref.[69]). Therefore, in patients with pulmonary arterial hypertension, obstructive sleep apnea should be ruled out by polysomnography. If obstructive sleep apnea is present, use of a continuous positive airway pressure (CPAP) device is the treatment of choice. Pulmonary arterial hypertension may improve with effective treatment of obstructive sleep apnea with CPAP.[69]

High altitude

Periodic breathing commonly occurs at high altitude.[70] The cycle of periodic breathing is short in contrast to the long cycle of periodic breathing in heart failure.

The underlying mechanism of high-altitude periodic breathing is hypoxemia, which narrows the difference between eupneic P_{CO_2} minus apneic threshold P_{CO_2}, and increases hypocapnic chemosensitivity below the apneic threshold.[8] Furthermore, the quantity of periodic breathing during sleep at high altitude tends to be more in individuals with enhanced ventilatory response to hypercapnia and hypoxia.[71] The relation with hypercapnic ventilatory response resembles that reported in patients with heart failure.[36]

Inhalation of supplemental oxygen or a small amount of CO_2 decreases periodic breathing. Furthermore, administration of acetazolamide improves desaturation and ameliorates the symptoms of acute mountain sickness in man at high altitude.[72,73] As discussed earlier, acetazolamide[8] widens the difference between the 2 P_{CO_2} set points (in contrast to hypoxemia) resulting in improvement of periodic breathing at high altitude.

Poststroke

Several studies[74–82] have shown that patients with stroke (acute, chronic, ischemic, nonischemic) have obstructive and central sleep apnea. Although obstructive sleep apnea could either precede (cause or contribute to the development of) or be caused by stroke, central apneas are most probably caused by the stroke and may decrease with time.[79]

A pattern of breathing similar to Hunter-Cheyne-Stokes breathing has also been reported in patients with stroke.[80–83] This pattern of breathing seems to have no relation to the site of pathology. Systolic heart failure should be considered in such patients.

Hypercapnic Central Sleep Apnea

These heterogeneous disorders are characterized by daytime steady-state hypercapnia or a P_{CO_2} level close to the upper normal limit. According to the alveolar ventilation equation, Pa_{CO_2} is directly proportional to CO_2 production and inversely proportional to alveolar ventilation. In these disorders, the increase in Pa_{CO_2} is caused by decreased global ventilation, and therefore the term hypoventilation is appropriate.[4] However, hypoventilation and hypercapnia become profound during sleep. Normally with the removal of the wakefulness drive to breathe, ventilation decreases with sleep onset and P_{CO_2} rises slightly. However, such a small physiologic decrease in ventilation results in a large increase in P_{CO_2}, if hypercapnia is already present; this is dictated by the alveolar ventilation equation and has to do with the hyperbolic relation of P_{CO_2} with alveolar ventilation.[4] Furthermore, in the presence of hypercapnia, if an arousal occurs, because of return of the wakefulness drive to breathe, ventilation increases somewhat but P_{CO_2} decreases considerably (this is referred to as increased plant gain). The increased plant gain increases the probability of developing central apnea if the apneic threshold P_{CO_2} is also increased.[84]

Another pathophysiologic consequence of sleep-induced hypercapnia is the development of severe desaturation. When P_{CO_2} rises considerably, severe hypoxemia ensues, given the reciprocal relation between alveolar P_{CO_2} and P_{O_2}.

In some of the disorders in this category, the pathologic process involves brainstem medullary respiratory centers responsible for automatic breathing (either for anatomic or functional reasons, eg, use of opioids). Consequently, when the wakefulness drive to breathe is absent, central apneas occur during sleep.

REM sleep may be associated with central sleep apnea in neuromuscular disorders involving the diaphragm. During REM sleep, there is costal muscle atonia and the diaphragm is the only inspiratory thoracic pump muscle active. Therefore, with diaphragmatic weakness or paralysis, during REM sleep, airflow ceases, and thoracoabdominal tracings look like central apnea. This is a pseudo central apnea and may occur in a variety of disorders associated with diaphragmatic paralysis.

Alveolar hypoventilation syndromes with normal pulmonary function

These central nervous system disorders are characterized by chronic alveolar hypoventilation with daytime hypercapnia, diminished or absent CO_2 chemosensitivity, and normal pulmonary function.

These disorders could be either genetic (congenital central hypoventilation syndrome and perhaps primary hypoventilation syndrome) or acquired (a variety of brainstem and spinal cord disorders). The unique feature of all of these disorders, however, is the failure of automatic/metabolic control of breathing that becomes manifest during sleep (Ondine curse) when breathing is controlled by the automatic/metabolic pathway. If this pathway is defective, ventilation decreases dramatically and hypoventilation and central apneas could occur.

Congenital central hypoventilation syndrome Congenital central hypoventilation syndrome (CCHS), a rare genetic disorder,[85–94] has gained considerable attention because of the recent discovery of its genetic basis.[89–92] The disorder is associated with other neurocristopathies such as Hirschsprung disease, which is caused by segmental colonic

aganglionosis. The disorder manifests itself after birth.

Primary (idiopathic) alveolar hypoventilation syndrome Primary (idiopathic) alveolar hypoventilation syndrome is usually a disorder of adult men diagnosed in the third or fourth decade. This disorder is characterized by chronic hypercapnia without any demonstrable neuromuscular, thoracic, pulmonary, or central nervous system pathology. The mechanisms leading to chronic hypercapnia in primary alveolar hypoventilation syndrome are not understood and they could have a genetic basis, similar to CCHS.

There are several therapeutic options for the treatment of CCHS and idiopathic chronic alveolar hypoventilation syndrome. These include nocturnal oxygen therapy, diaphragmatic pacing and mechanical ventilation by mask, via tracheotomy, or by negative pressure ventilation.[86,95–106] Respiratory stimulants are generally ineffective.[107]

Oxygen therapy may further increase P_{CO_2}, diaphragmatic pacing or negative pressure ventilation may unmask or result in upper airway occlusion during sleep necessitating tracheotomy. However, a positive airway pressure device should be the first choice. Although no trials have been performed, the new generation noninvasive adaptive servoventilation devices should be effective in treating hypoventilation and central sleep apneas.

Brainstem and spinal cord disorders

Brainstem and spinal cord disorders constitute several heterogeneous pathologic processes that could result in severe hypoventilation and central apnea during sleep. With regard to brain stem pathology, this is not surprising, because central chemoreceptors and respiratory centers are located in this region. Various pathologic processes such as compression, edema, ischemia, infarct, tumor, encephalitis, neurodegenerative disorders and Chiari malformation have been associated with central sleep apnea.[108–115]

Cervical cordotomy[116] and anterior cervical spinal artery syndrome[117] result in automatic failure of breathing. In these 2 conditions, the process involves the descending pathways subservient to the automatic control of breathing with preservation of the voluntary pathway. Therefore, during sleep when the wakefulness drive to breathe ceases, hypoventilation and central apnea occur (Ondine curse). This phenomenon is in a way similar to CCHS.

For treatment of central apneas and hypoventilation in this category, therapy should be individualized. Several modalities including bilevel ventilation in time mode, tracheostomy with mechanical ventilation, or diaphragm pacing could be used.

Neuromuscular disorders

This category (see **Box 1**) includes a large number of neuromuscular disorders that may affect respiratory muscles (muscular dystrophies such as myotonic dystrophy, idiopathic diaphragmatic paralysis), the neuromuscular junction (myasthenia gravis), and phrenic and intercostal nerves (amyotrophic lateral sclerosis).[118]

Depending on the site of pathology, a specific pathophysiologic breathing disorder could occur during sleep. With diaphragmatic involvement, however, breathing is particularly compromised in REM sleep when hypoventilation and what appears to be a central apnea on a polysomnograph (discussed earlier) may occur. In disorders that involve the pharyngeal muscles, obstructive apneas and hypopneas may occur during sleep.

In neuromuscular disorders, as respiratory muscle weakness progresses and daytime hypercapnia develops, sleep-related breathing disorders present with more severe hypoventilation hypercapnia, more severe desaturation, and perhaps more central apneas. These phenomena have to do with where P_{CO_2} resides on the hyperbolic curve of the alveolar ventilation equation discussed earlier.

Treatment of sleep-related breathing disorders in neuromuscular diseases should be individualized.[118–122] Two important factors determining the modality of therapy include the presence of impaired rhythmogenesis and upper airway obstruction during sleep. Use of bilevel ventilation could be extremely helpful for patients with hypercapnia if the brainstem is not involved. If rhythmogenesis is impaired and upper airway obstruction is present during sleep, tracheostomy with assisted ventilation may become necessary. However, bilevel ventilation with back up rate and new generation pressure support servoventilators should be extremely effective.

Opioids

Ventilatory depression during wakefulness is a well-known effect of opioid drugs. However, with chronic use, daytime hypoventilation is generally mild, but sleep apnea is quite prevalent.[123–127] In a case-control study[125] of 60 patients taking opioids for pain management, matched for age, gender, and body mass with 60 patients not taking opioids, the former group had a significantly higher AHI than the control group, primarily because of an increase in the number of central apneas. In a large study of patients in a pain clinic, Webster and associates[126] routinely recommended polysomnography to 392 consecutive subjects. Of the 140

subjects who underwent polysomnography in their institution, 75% had an AHI of 5/h or more, 50% had an AHI of 15/h or more, and 36% had severe sleep apnea with an AHI of 30/h or more. Opioids use is associated with a mixed pattern of sleep-disordered breathing (presence of central and obstructive events) although central apneas commonly predominate.

In the last few years, there has been a dramatic change in the management of chronic pain associated with a marked acceleration in the use of opioids. Given the high prevalence of sleep apnea in this population, a large number may suffer from significant unrecognized sleep apnea. Sleep apnea probably contributes to excess unexplained mortality associated with the use of opioids as many are discovered dead in the morning or in bed during the day.

The mechanisms of opioid-induced sleep apnea are best explained by the model of 2 respiratory rhythm generators that are anatomically distinct but coupled.[127] The inspiratory rhythm generator is located in the pre-Botzinger complex, whereas the expiratory rhythm generator is located in the retrotrapezoid nucleus/parafacial respiratory group. In this model, the pre-Botzinger complex neurons are inhibited by opioids but the expiratory motor neurons remain unaffected. Opioids inhibit discharge of inspiratory neurons in the pre-Botzinger complex, resulting in central apneas. In these experiments, genioglossus muscle activity also decreased consistent with the observation that opioids can cause obstructive sleep-disordered breathing events.

Treatment of opioid-induced sleep apnea is difficult because of the simultaneous presence of obstructive sleep apnea and central sleep apnea, with the latter being resistant to CPAP.[128] A preliminary study[129] showed that a new generation pressure support servoventilator could be promising.

Central Sleep Apnea in Endocrine Disorders

Central sleep apnea has been observed in 2 endocrine disorders: acromegaly and hypothyroidism. In both disorders, obstructive sleep apnea is the predominant form.

Acromegaly

Several studies have reported a relatively high prevalence of sleep apnea in patients with acromegaly.[130–132] Obstructive and central sleep apneas occur. Excess pharyngeal soft tissue (caused by cellular hyperplasia, excess connective tissue, and extracellular water) and macroglossia could account for obstructive sleep apnea, which may contribute to the high prevalence and progression of cardiovascular disease of acromegaly.[132] Obstructive sleep apnea should be treated with CPAP, although treatment with octreotide (a somatastatin analogue) could result in tissue regression and improvement in sleep apnea.[130,133,134] However, this may take several months, and sleep apnea may persist in spite of therapy for acromegaly.

Studies have shown that patients with acromegaly also suffer from central sleep apnea, and this correlated with the levels of human growth hormone, insulinlike growth factor 1, and hypercapnic ventilatory response.[130,133,135] The enhanced ventilatory response could increase the likelihood of developing central sleep apnea. Treatment with octreotide also improved central sleep apnea.[133]

Hypothyroidism

Similar to acromegaly, obstructive and central sleep apneas occur in patients with hypothyroidism, although central sleep apnea is much less frequent than obstructive apneas.[136,137] The mechanisms of central sleep apnea are not understood, but excess pharyngeal soft tissue, similar to acromegaly could account for obstructive sleep apnea.

Central Sleep Apnea with Obstructive Sleep Apnea

Few central apneas are observed in polysomnograms of patients with obstructive sleep apnea and are appropriately ignored because they are of no clinical significance. However, some patients referred for evaluation of obstructive sleep apnea may have excess central apneas or develop central sleep apnea during initiation of CPAP therapy. These include patients with severe obstructive sleep apnea, those with systolic heart failure, atrial fibrillation, neuromuscular disorders, or on opioids.

The presence of central sleep apnea (CAI $\geq$5/h) on CPAP could therefore be emergent (ie, not present on a diagnostic polysomnograph) or considered persistent (central sleep apnea is present on a diagnostic polysomnograph). Such patients commonly continue to have obstructive and central sleep apnea on CPAP and this has been referred to as complex sleep apnea with an estimated prevalence of 5% to 20%[129,138–140]; most recent studies[129,141,142] show a prevalence of about 5% to 6%.

In our study,[129] which included 1286 patients referred for evaluation of obstructive sleep apnea, the monthly incidence of central sleep apnea during initial CPAP titration (CPAP1) varied from 3% to 10% during a 1-year period, with an average of 6.5%. An important part of this study has to do with determination of the natural history of central

sleep apnea on CPAP. Of the 42 patients who developed CPAP1, central sleep apnea was eliminated in most of them with long-term use of CPAP (average time/night = 5.6 hours). However, 9 of the 42 patients (an estimated 1.5% of 1286 patients with obstructive sleep apnea) had persistent central sleep apnea with long-term use of CPAP. This observation is consistent with the results of 2 long-term studies[143,144] with tracheotomy. Guilleminault and colleagues[143] noted that patients with obstructive sleep apnea who underwent tracheostomy initially had central sleep apnea. However, a repeat polysomnograph after a period of time showed the number of central apneas had decreased. Coccagna and colleagues[144] reported a similar observation. In the study of Dernaika and colleagues[139] most of the central sleep apneas resolved in 12 of the 14 patients with CPAP1 who had a repeat titration polysomnogram 9 weeks after their initial polysomnogram, resulting in a prevalence of CPAP-persistent central sleep apnea of about 1.5%, the prevalence observed in our study.[129]

Central Sleep Apnea with Upper Airway Disorders

The nose, larynx, and pharynx are replete with receptors[145,146] and animal and preterm infants studies[146–150] have shown that stimulation of upper airway receptors may cause central apnea. Apnea may be produced by water, chemical, or mechanical stimulation of these receptors.

Studies in normal adults[151,152] have shown that nasal obstruction results in central apneas. This finding has not been reproduced in allergic rhinitis, however. McNicholas and colleagues[153] studied 7 subjects when asymptomatic and during exacerbation of allergic rhinitis; CAI did not change significantly, although the obstructive apnea index increased significantly.

High-frequency (30 Hz) low-pressure ventilation[154] and CPAP[155,156] have been shown to improve central sleep apnea suggesting that upper airway receptors and closure may induce central apnea in humans.

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